

## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION  
(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
US Department of Commerce  
United States Patent and Trademark  
Office, PCT  
2011 South Clark Place Room  
CP2/5C24  
Arlington, VA 22202  
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 19 July 2001 (19.07.01)	
International application No. PCT/US00/28713	Applicant's or agent's file reference 40999
International filing date (day/month/year) 17 October 2000 (17.10.00)	Priority date (day/month/year) 18 October 1999 (18.10.99)
<b>Applicant</b> FRANK, R., Keith	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

30 April 2001 (30.04.01)

in a notice effecting later election filed with the International Bureau on:

\_\_\_\_\_

2. The election  was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer  Odile ALIU  Telephone No.: (41-22) 338.83.38
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(12) INTERNATIONAL APPL

ON PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
26 April 2001 (26.04.2001)

PCT

(10) International Publication Number  
**WO 01/28567 A3**

- (51) International Patent Classification<sup>7</sup>: A61K 31/662. (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, YU, ZA, ZW.
- (21) International Application Number: PCT/US00/28713
- (22) International Filing Date: 17 October 2000 (17.10.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
60/160,019 18 October 1999 (18.10.1999) US
- (71) Applicant (for all designated States except US): THE DOW CHEMICAL COMPANY [US/US]: 2030 Dow Center, Midland, MI 48674 (US).
- (72) Inventor: and
- (75) Inventor/Applicant (for US only): FRANK, R., Keith [US/US]: 213 Pansy Path, Lake Jackson, TX 77566 (US).
- (74) Agent: KARADZIC, Dragan, J.; Intellectual Property, B-1211, 2301 N. Brazosport Boulevard, Freeport, TX 77541 (US).
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:  
— with international search report
- (88) Date of publication of the international search report: 29 November 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

**WO 01/28567 A3**

(54) Title: AMINOALKYLENEPHOSPHONATES FOR TREATMENT OF BONE DISORDERS

(57) Abstract: A method for preventing or minimizing loss of bone mineral in mammals which method comprises administering to a mammal an amount of an aminoalkyleneephosphonate which is effective to prevent or minimize loss of bone mineral density. The aminoalkyleneephosphonates of the present invention should have at least one R-N(Alk-PO<sub>3</sub>H<sub>2</sub>)<sub>2</sub> group or at least two RRN-Alk-PO<sub>3</sub>H<sub>2</sub> groups wherein R and R can be, same or different, aliphatic or cyclic moiety, and Alk is an alkylene group having from 1 to 4 carbon atoms.

V

**PATENT COOPERATION TREATY**  
**PCT**

**INTERNATIONAL SEARCH REPORT**

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference  40999	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No.  PCT/US 00/ 28713	International filing date (day/month/year)  17/10/2000	(Earliest) Priority Date (day/month/year)  18/10/1999
Applicant  THE DOW CHEMICAL COMPANY et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
  - contained in the international application in written form.
  - filed together with the international application in computer readable form.
  - furnished subsequently to this Authority in written form.
  - furnished subsequently to this Authority in computer readable form.
  - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
  - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2.  Certain claims were found unsearchable (See Box I).

3.  Unity of invention is lacking (see Box II).

4. With regard to the **title**,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-5,10-14 relate to a compound defined (*inter alia*) by reference to the following parameter(s): aminoalkylenephosphonate, "aminoalkylenephosphonate with at least one R-N(ALK-PO<sub>3</sub>H<sub>2</sub>)<sub>2</sub>", "aminoalkylenephosphonate where the amine moiety of the aminoalkylenephosphonate represented by... is derived from either an aliphatic...", "aminomethylenephosphonate" et cetera. The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the compounds mentioned in claims 6-9 and in the examples at page 7 and 10.

Claims searched completely: 6-9, 15-18.

Claims searched incompletely: 1-5,10-14.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

International Application No

US 00/28713

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 A61K31/662 A61P19/08

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, MEDLINE, SCISEARCH, WPI Data, PAJ

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 902 825 A (JIA WEI) 11 May 1999 (1999-05-11) column 1, paragraph 2 column 6, paragraph 4 column 2, paragraph 5 column 4, line 36 - line 39 column 5, paragraph 5 - paragraph 8 column 7, paragraph 1 claims 1,6 ---- -/-/	1-5,7, 10-14,16

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

15 August 2001

28/08/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
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Authorized officer

Bonzano, C

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/28713

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>MILLER S C ET AL: "EFFECTS OF N N N' N' ETHYLENEDIAMINETETRAMETHYLENE PHOSPHONIC-ACID AND 1 HYDROXYETHYLIDENE-1,1-BISPHOSPHONIC-ACID ON CALCIUM ABSORPTION PLASMA CALCIUM LONGITUDINAL BONE GROWTH AND BONE HISTOLOGY IN THE GROWING RAT" TOXICOLOGY AND APPLIED PHARMACOLOGY, vol. 77, no. 2, 1985, pages 230-239, XP001014788  ISSN: 0041-008X  page 230, column 1, paragraph 1 -column 2, paragraph 2  page 231, column 1, paragraph 3  page 238, column 1, paragraph 3 -column 2, paragraph 1  ---</p>	1-5, 10-14
X	<p>JEE W S S ET AL: "EFFECTS OF N N N' N' ETHYLENEDIAMINETETRAMETHYLENE PHOSPHONIC ACID ON CORTICAL BONE REMODELING IN THE ADULT DOG" TOXICOLOGY AND APPLIED PHARMACOLOGY, vol. 92, no. 3, 1988, pages 335-342, XP001014791  ISSN: 0041-008X  page 335, column 1, line 1 -page 336, column 1, line 1  page 340, column 2, paragraph 2  ---</p>	1-5, 10-14
X	<p>MOORE N C ET AL: "Effects of intraperitoneal administration of hexasodium N,N,N',N'-ethylenediaminetetramethylenephosphonate on rat bone metabolism." FUNDAMENTAL AND APPLIED TOXICOLOGY, (1990 APR) 14 (3) 491-501. , XP001014568  page 499, column 1, paragraph 3 -column 2, paragraph 1  ---</p>	1-5, 10-14
A	<p>DATABASE CHEMABS 'Online!  CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US;  WANG, WENJIA ET AL: "Effect of TATMP 'N,N',N',N''-tetrakis(phosphonomethyl)-1,4,7,10-tetraazacyclododecane! on the growth kinetics of calcite crystals"  retrieved from STN  Database accession no. 113:14960  XP002174221  abstract  &amp; SHUICHULI JISHU (1989), 15(6), 370-3 ,  ---  ---</p>	7,16

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/28713

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 00145 A (DOW CHEMICAL CO ;LYNCH SAMUEL E (US); PRIBISH JAMES R (US); GARLIC) 6 January 1994 (1994-01-06) page 1, paragraph 1 – paragraph 2 page 7; figure 4 page 6, line 15 –page 7, line 35 claim 14 ---	7,16
A	EP 0 411 941 A (DOW CHEMICAL CO) 6 February 1991 (1991-02-06) column 2, paragraph 6 column 1, paragraph 1 ---	7,16
A	US 5 385 893 A (KIEFER GARRY E) 31 January 1995 (1995-01-31) example F claims 23-27 ---	8,17
A	US 5 714 604 A (KIEFER GARRY E) 3 February 1998 (1998-02-03) column 1, paragraph 1 – paragraph 2 column 2, line 41 –column 3, line 20 example 17 -----	8,17

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/US 00/28713

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 5902825	A 11-05-1999	AU 5491398 A		03-08-1998
		EP 0952854 A		03-11-1999
		WO 9830246 A		16-07-1998
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WO 9400145	A 06-01-1994	US 5505931 A		09-04-1996
		AU 4660093 A		24-01-1994
		CA 2139323 A		06-01-1994
		CN 1092076 A		14-09-1994
		EP 0653941 A		24-05-1995
		FI 946156 A		27-02-1995
		HU 71220 A		28-11-1995
		JP 7508979 T		05-10-1995
		MX 9303963 A		31-01-1995
		NO 945093 A		27-02-1995
		AU 6020494 A		26-09-1994
		CA 2157402 A		15-09-1994
		EP 0687261 A		20-12-1995
		JP 8507517 T		13-08-1996
		WO 9420487 A		15-09-1994
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EP 0411941	A 06-02-1991	US 4937333 A		26-06-1990
		AP 163 A		11-01-1992
		AT 140459 T		15-08-1996
		AU 634267 B		18-02-1993
		AU 6023790 A		07-02-1991
		BG 60519 B		28-07-1995
		BR 1101174 A		08-08-2000
		BR 9003694 A		03-09-1991
		CA 2020950 A		05-02-1991
		CN 1049351 A, B		20-02-1991
		CN 1091744 A, B		07-09-1994
		DD 297414 A		09-01-1992
		DE 69027818 D		22-08-1996
		DE 69027818 T		21-11-1996
		DK 411941 T		11-11-1996
		EG 19250 A		29-09-1994
		ES 2090105 T		16-10-1996
		FI 105033 B		31-05-2000
		FI 954391 A		18-09-1995
		GR 3020932 T		31-12-1996
		HK 1007558 A		16-04-1999
		HU 54698 A, B		28-03-1991
		IE 902812 A		27-02-1991
		IL 95094 A		26-05-1995
		IL 110861 A		14-07-1999
		JP 2922263 B		19-07-1999
		JP 3066697 A		22-03-1991
		KR 178779 B		15-05-1999
		KR 178877 B		15-05-1999
		LV 10718 A		20-06-1995
		LV 10718 B		20-04-1996
		NO 178196 B		30-10-1995
		NO 940643 A		05-02-1991
		NO 952161 A, B,		05-02-1991
		NO 964191 A		17-10-1990
		NO 970653 A		05-02-1991
		NZ 234464 A		27-06-1994
		NZ 247888 A		26-07-1994

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

/US 00/28713

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0411941 A		OA 9300 A PH 26901 A PL 166453 B PL 164908 B PT 94188 A,B RO 105967 B SK 379690 A SU 1838321 A ZA 9005564 A	15-09-1992 03-12-1992 31-05-1995 31-10-1994 18-04-1991 30-01-1993 03-06-1998 30-08-1993 25-03-1992
US 5385893 A	31-01-1995	AU 687400 B AU 6784994 A BG 100194 A CN 1125906 A EP 0697872 A FI 955336 A HU 72649 A JP 8511003 T LV 11429 A LV 11429 B NO 954441 A PL 311649 A SG 46496 A WO 9426276 A	26-02-1998 12-12-1994 31-12-1996 03-07-1996 28-02-1996 22-12-1995 28-05-1996 19-11-1996 20-08-1996 20-04-1997 05-01-1996 04-03-1996 20-02-1998 24-11-1994
US 5714604 A	03-02-1998	AP 543 A AT 172978 T AU 682190 B AU 6908694 A BG 62775 B BG 100193 A CN 1125949 A,B CZ 9502890 A DE 69414382 D DK 698029 T EE 3159 B EG 20296 A EP 0698029 A ES 2123137 T FI 955281 A HK 1014537 A HU 73142 A JP 8510249 T LT 1925 A,B LV 10867 A,B NO 954439 A PL 311651 A RO 115883 B RU 2135507 C WO 9426753 A ZA 9403158 A	09-10-1996 15-11-1998 25-09-1997 12-12-1994 31-07-2000 31-12-1996 03-07-1996 13-03-1996 10-12-1998 19-07-1999 15-12-1995 31-10-1998 28-02-1996 01-01-1999 20-12-1995 19-05-2000 28-06-1996 29-10-1996 31-01-1995 20-10-1995 05-01-1996 04-03-1996 28-07-2000 27-08-1999 24-11-1994 06-11-1995

PATENT COOPERATION TREATY  
PCT

REC'D 27 FEB 2002  
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) *7*

Applicant's or agent's file reference  40999	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No.  PCT/US00/28713	International filing date (day/month/year)  17/10/2000	Priority date (day/month/year)  18/10/1999
International Patent Classification (IPC) or national classification and IPC  A61K31/662		
Applicant  THE DOW CHEMICAL COMPANY et al.		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li>I    <input checked="" type="checkbox"/> Basis of the report</li> <li>II    <input type="checkbox"/> Priority</li> <li>III    <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li>IV    <input type="checkbox"/> Lack of unity of invention</li> <li>V    <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li>VI    <input type="checkbox"/> Certain documents cited</li> <li>VII    <input type="checkbox"/> Certain defects in the international application</li> <li>VIII    <input type="checkbox"/> Certain observations on the international application</li> </ul>		

Date of submission of the demand  30/04/2001	Date of completion of this report  22.02.2002
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Heller, D  Telephone No. +49 89 2399 8746



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/28713

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-10                  as originally filed

**Claims, No.:**

1-18                  as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description,        pages:
- the claims,              Nos.:
- the drawings,          sheets:

5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/28713

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
  - the entire international application.
  - claims Nos. 1-14.

because:

- the said international application, or the said claims Nos. 1-9 (concerning industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
  - the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
  - the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
  - no international search report has been established for the said claims Nos. 1-5, 10-14.
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
    - the written form has not been furnished or does not comply with the standard.
    - the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N) Yes: Claims 6, 8, 9, 15, 17, 18  
No: Claims 1-5, 7, 10-14, 16

Inventive step (IS) Yes: Claims  
No: Claims 1-18

Industrial applicability (IA) Yes: Claims see sections III and V

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US00/28713

No: Claims

2. Citations and explanations  
**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/28713

**SECTION III:**

Since claims 1 to 5 and 10 to 14 relate to a large number of possible compounds, the search has been carried out for those parts of the claims relating to the compounds mentioned in claims 6 to 9 and 15 to 18 as well as for the general idea underlying the application. The EPO policy, when acting as an International Preliminary Examining Authority, is not to carry out a preliminary examination on matter which has not been searched (Rule 66.1 (e) PCT). Therefore, the preliminary examination has been carried out on whole the subject-matter of claims 6 to 9 and 15 to 18 which has been searched.

Claims 1 to 9 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**SECTION V:**

**Prior art**

Reference is made to the following documents:

D1 (US-A-5 902 825) directed to a composition and method of using the same for the palliation of pain in patients having diseases affecting the bone and bone joints including metastatic bone cancer, rheumatic diseases such as rheumatoid arthritis, osteoarthritis and other inflammatory arthropathies (col. 1, ll. 8 to 13).

D2 (WO 94 00145 A) relates to specific target delivery systems; namely, delivery of growth promoting factors to bone for its regeneration by a chelating composition system (p. 1, ll. 2 and 3).

D3 (EP-A-0 411 941) describes that certain of the methylenephosphonated amines are useful for imaging and other radiopharmaceutical uses when complexed as chelates with radioactive metals (col. 2, ll. 6 to 11).

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/28713

D4 (US-A-5 385 893) is directed to novel ligands that are tri- and tetra-cyclopolyazamacro-cyclic compounds, and derivatives thereof (col. 2, II. 65 to 67).

D5 (US-A-5 714 604) concerns a process for the preparation of azamacrocyclic or acyclic aminophosphonate ester derivatives. Such process provides ligands which are useful as diagnostic or therapeutic agents (col. 1, II. 6 to 9).

D6 (Miller S.C. et al.) relates to the effects of EDTMP on the calcium absorption, plasma calcium, longitudinal growth and bone history in rats (title).

D7 (DATABASE CHEMABS; Wang W. et al.) discloses the effects of DOTMP on the growth of calcite crystals *in vitro* (title).

D8 (Jee W.S.S. et al.) relates to the effects of EDTMP on cortical bone remodeling in dogs (title).

D9 (Moore N.C. et al.) discloses the effects of i.p. administered EDTMP on rat bone metabolism (title)

**Novelty**

The subject-matter of claims 1 to 5, 7 and 10 to 14 and 16 is not new in the sense of Article 33 (2) PCT.

As D1 already discloses the use of aminoalkylenephosphonate - especially of AMP and DOTMP (col. 6, II. 51 to 67) - for the treatment of diseases which affect the bone (col. 5, II. 34 to 48), claims 1 to 5, 7 and 10 to 14 and 16 are not novel over D1.

D6 discloses the effects of EDTMP on plasma concentrations, intestinal calcium absorption, longitudinal bone growth, growth plate thickness, osteoid accumulation and quantity of mineralized tissue (p. 231, col. 1, §3). Therefore, D6 anticipates novelty of present claims 1 to 5 and 10 to 14.

D8 discloses same the effects of EDTMP as described in D6, but in dogs, not in rats (p. 340, col. 2, §2). Therefore, claims 1 to 5 and 10 to 14 are not novel over D8.

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D9 is directed to the same subject-matter as D6 and D8. It therefore, anticipates novelty of present claims 1 to 5 and 10 to 14.

As D2 is directed to a complex of DOTMP and a growth factor (GF) for regenerating bone (claim 29), and not to the compound without the GF as claimed in the present claims, D2 does not seem to anticipate novelty of present claims.

D3 discloses the same substances as claimed - mainly DOTMP (cf. examples 11 to 19) -, but not for the claimed treatment and does therefore not anticipate novelty of present claims 1 to 18.

D4 relates to BP2MP as chelating agent for use in therapy (col. 2, ll. 39 to 62). For D4 applies the same as for D3.

For D5 applies the same as for D3 and D4.

As the effects disclosed in D7 are described only for *in vitro* tests, D7 is not relevant for novelty.

**Inventive step**

The subject-matter of claims 1 to 18 does not involve an inventive step in the sense of Article 33 (3) PCT.

*For claims 1 to 5, 7 and 10 to 14 and 16 the following applies:*

Even if the applicant is able to establish novelty it cannot be seen that any particular aspect of the application as filed would involve an inventive step under Article 33 (3) PCT in the light of the relevant prior art.

*For claims 6, 8 and 9 as well as corresponding claims 15, 17 and 18 the following applies:*

The additional features of said claims can be determined as alternatives and are therefore not inventive in the sense of Article 33 (3) PCT over the cited prior art.

**Industrial applicability**

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For the assessment of the present claims 1 to 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-5,10-14 relate to a compound defined (*inter alia*) by reference to the following parameter(s): aminoalkylenephosphonate, "aminoalkylenephosphonate with at least one R-N(ALK-PO<sub>3</sub>H<sub>2</sub>)<sub>2</sub>", "aminoalkylenephosphonate where the amine moiety of the aminoalkylenephosphonate represented by... is derived from either an aliphatic...", "aminomethylenephosphonate" et cetera.

The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the compounds mentioned in claims 6-9 and in the examples at page 7 and 10.

Claims searched completely: 6-9, 15-18.

Claims searched incompletely: 1-5,10-14.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.